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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 07/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/733,878	GIRARD ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-212* is/are pending in the application.

4a) Of the above claim(s) *5,6,8-18 and 20-212* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 December 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group VII in the reply filed on May 22, 2006 is acknowledged. The traversal is on the ground(s) that groups I-LXVIII can be searched and examined together without serious burden because they are all directed to similar, significantly overlapping subject matter (Applicant's response, page 2-4). This is not found persuasive because while Applicant indicates that the claims of Groups I-LIVIII are all drawn to methods of modulating the expression of a gene that is responsive to a THAP-family polypeptide (Applicant's response, page 3, 2nd parag.), the binding of one protein, THAP, to DNA is structurally and functionally distinct and different from two proteins binding to DNA (THAP and a chemokine). The THAP/chemokine complexes have been restricted into individual inventions based on the fact that each chemokine is structurally and functionally different and distinct from each other. While there is a common theme of the complexes involving THAP and DNA, the inventions are each distinct from each other because THAP will bind different DNA sequences and/or will effect different transcriptional activities from that of a THAP/chemokine complex. With regard to THAP and each different chemokine, each combination of THAP and chemokine will result in different DNA binding targets and/or different transcriptional activities following protein/DNA complex formation. The search for THAP may be overlapping in some respects with THAP/chemokine. However, the search is not coextensive and the analysis involved in examining a THAP-DNA complex is different from that of a

THAP/chemokine-DNA complex. Further, the analysis involved in examining THAP with each different and distinct chemokines is independent and distinct because each THAP/chemokine complex will have different and unique functional activity. As such, the groups remain separated. With regard to the issue of linking claims, Applicant indicates, that the Examiner must also assess the patentability of generic linking claim 1 (see MPEP 809) (Applicant's response, page 3, 2nd parag.) and must search for prior art that describes both methods of enhancing and methods of repressing gene expression by modulating the interaction between a nucleic acid and THAP-family polypeptide, wherein the THAP-family polypeptide is either bound or unbound to a protein binding partner, such as chemokine. As a result, searching the entire scope of claim 1 would reveal the art relevant to the patentability of generic linking claims 20 and 38 (related to THAP/chemokine complexes) (Applicant's response, page 3, 2nd parag. and page 4, 1st parag.). In response, the linking claims will be included in the analysis in this Office Action. However, per the Restriction Requirement, December 21, 2005, a search and examination of Groups I-VI and VIII-LXVIII is not required. Applicant is reminded that rejoinder of the unelected inventions can occur following allowance of the linking claim and claim(s) depending from or otherwise requiring all the limitations of an allowable linking claim will be entered as a matter of right (see MPEP 809.03).

The requirement is still deemed proper and is therefore made FINAL.

Claims 5, 6, 8-18, 20-212 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Groups, there

being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on May 22, 2006.

Claims 1-5, 7, 19 are under consideration. Per Restriction Requirement of December 21, 2005, the Invention is drawn to a method of modulating expression of a THAP-responsive gene, said method comprising modulating the interaction of a THAP-family polypeptide or a biologically active fragment thereof with a nucleic acid, thereby repressing expression of said THAP-responsive gene, wherein the nucleic acid is THRE and wherein the THAP-responsive gene encodes a polypeptide involved in inflammatory disease.

Information Disclosure Statement

Applicant filed Information Disclosure Statements (IDSes) on November 22, 2004, March 11, 2005, and May 16, 2005. The IDS filed May 16, 2005 has been considered by the Examiner. However, the IDSes filed November 22, 2004 and March 11, 2005 have not been considered, as follows.

The information disclosure statement filed November 22, 2004 and March 11, 2005 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. In the November 22, 2004 IDS, Citation No. 193 (page 9/25), Farber J., 1993 has not been considered because no copy has been provided. In order for this publication to be

considered, Applicant must provide a copy of the publication. Citation No. 481 (page 21/25), Sgadari et al., 1997, is missing pages of the text. In order for this publication to be considered, Applicant must provide a copy of the publication. In the March 11, 2005 IDS, none of the Non Patent Literature documents (Nos. 4-7) were provided. In order for these publications to be considered, Applicant must provide copies of these publications.

The information disclosure statement filed November 22, 2004 fails to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. The information disclosure statement has been placed in the application file, but the information referred to therein has not been considered. In the November 22, 2004 IDS, U.S. Patent document No. 18 (page 1/25), 5,219,089, Kiolbasa et al., has not been considered. The patent is to cardboard box construction. It is unclear what the relevance of the patent is to the instant invention. As such, the patent has not been considered. Foreign Patent document No. 60 (page 3/25) WO 92/20702, has not been considered. The document is to a transient electromagnetic method. It is unclear what the

relevance of the document is to the instant invention. As such, the citation has not been considered. Non-patent literature citation, No. 87 (page 4/25), Amersham Biosciences, is missing a year of publication and has not been considered. It is also unclear from the submitted document what the year of publication is. Citation No. 132, Bradley, A. has not been considered as the citation is missing a year of publication. It is also unclear from the publication what the year of publication is. Citation No. 150 appears to be the same as citation No. 153 (page 7/25). As such, citation No. 150 has been lined through and has been indicated as a duplicate ("dup"). Citation No. 153 is missing the issue number. Citation Nos. 219 and 221 (page 10/25) have not been considered. The references are missing dates. Citation No. 557 (page 24/25), Yang et al., is missing the year of publication. It is also unclear from the publication what the year of publication is.

The information disclosure statements filed November 22, 2004 and March 11, 2005 fail to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609, as described above. They have been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered. Pages 357-366 of the specification contain a listing of references. Since these have not been listed separately on an IDS, they have not been considered.

Drawings

New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because Figure 2, 3B, 4B, 7A, 14, 15, 20, 27, 28, 29 are dark. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Specification

37 CFR 1.821(d) states: "[w]here the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description of claims, even if the sequence is also embedded in the text or the description or claims of the patent application.

The nucleotide sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

Figure 18 comprises nucleic acid sequences that are more than 10 bases long. These sequences must be provided a SEQ ID NO. and the sequences must be provided in computer readable format (CRF) and on paper. Further, a statement indicating the CRF and paper sequences are the same must also be provided, see the attached notice to comply.

Appropriate correction is required.

The absence of proper sequence listing did not preclude the examination on the merits however, **for a complete response to this office action, applicant must submit the required material for sequence compliance.**

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7, 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a

way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The final Written Description Examination guidelines that were published on January 5, 2001 (66 FR 1099; available at http://www.uspto.gov/web/menu/current.html#register).

The written description requirement for a claimed genus is satisfied by sufficient description of a representative number of species by actual reduction to practice and by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show applicant were in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed."Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

At the time of filing, the specification teaches that the THAP domain (amino acids 1-89 of the amino terminus of human THAP1) structure was characterized via a SeqFold threading program and that the THAP domain appeared to have a topology similar to that of the D. melanogaster P-element

transpoase DNA binding domain (DBD) which shares a common topology with the DBD of nuclear receptors (specification, Example 20). The specification teaches that the DNA binding specificity was determined by using a random oligonucleotide selection and that the THAP domain is a site-specific DNA binding domain. In addition to DR5 motifs and ER11 motifs, the THAP domain also bound the THAP1-responsive element (THRE) (specification, Example 28, and 28B). The specification teaches that when human primary endothelial cells were transduced with THAP1, 23 candidate THAP1-target genes were downregulated in THAP-1 overexpressing cells, of which 9 genes were of unknown function, and 10 genes correspond to cell cycle/cell proliferation (CKS1, Survivin, PTTG1/Securin, PTTG1/Securin, PTTG2/Securin2, PTTG3/Securin3, MAD2L1, USP16, HMMR, KIAA0008, CDCA7, and THAP) (specification, Example 45). While the specification provides these teachings, the specification does not provide structural/functional guidance to arrive at claimed invention.

First, with regard to a method of repressing expression of aTHAP-responsive gene, wherein the gene is involved in inflammatory disease, while the specification teaches that a series of genes were downregulated when THAP-1 was overexpressed in endothelial cells, the specification teaches that these were genes that appeared to correspond to events in the cell cycle/cell proliferation (specification, Example 45). Nothing in the specification provides guidance that any genes associated with inflammatory disease was regulated by THAP1 overexpression. More particularly, nothing in the specification teaches that there is any relationship between THAP, THRE, and any inflammatory disease. As

such, the specification fails to provide any description for a gene associated with any inflammatory disease which is further regulated by THAP1. Second, the claims are drawn to a method of modulating the interaction between a THAP-family polypeptide or a biologically active fragment thereof and THRE, wherein changes in interaction results in repression of a gene associated with inflammation. However, nothing in the specification teaches that THAP has any transcriptional activity as an activator or as a repressor. As such, while the specification teaches that the THAP domain may have the ability to bind a specific sequence of DNA (for example, in an electrophoretic mobility shift assay, specification, Figure 25), the specification does not teach whether any THAP protein has a transcriptional repressor or activator such that an artisan could use THAP or any "biologically active fragment thereof" and monitor transcriptional activity.

Third, while the specification teaches that the human THAP1 domain (amino acids 1-89 of the amino terminus of human THAP1) was used to determine site-specific DNA binding sites and that the THAP domain was used to isolate 95 other sequences that appeared to have a THAP domain, and that the 95 sequences appeared to have a several amino acids that were conserved amongst them (specification, Figure 9C, underlined amino acids are conserved residues), the specification does not teach that these conserved residues are necessary within the structure of the domain for DNA binding activity. For example, it is unclear whether these amino acids are conserved for an entirely unrelated reason, such as protein interaction. As such, while the specification

illustrates the ability of amino acids 1-89 of human THAP1 to bind DNA, the example does not enable an artisan to expect that several conserved amino acids amongst proteins would necessarily have the same structure and biological activity between proteins.

The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision all the possible variant amino acid sequences that comprise a functional THAP-family protein or a functional THAP domain, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method used. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of identifying it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were

found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, no THAP protein, no biologically active fragment, and no THAP responsive nucleic acid encoding a polypeptide involved in inflammatory disease meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1-5, 7, 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many

factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

As indicated above in the Written Description, above, while the specification provides specific teachings that characterize human THAP1, a human THAP domain, and the potential biological role(s) that THAP1 has, the specification does not provide specific guidance for an artisan to practice the claimed invention.

The claimed method is drawn to a method of repressing expression of a THAP responsive gene, wherein the method comprises modulating the interaction of a THAP-family polypeptide or a biologically active fragment thereof with a nucleic acid, which thereby represses expression of a said THAP responsive gene. While the specification provides guidance that the THAP domain appears to have a DNA binding domain (DBD) similar to that of Drosophila P-element transposase and that a screen identified putative DNA binding sites for the THAP domain and that an overexpression of THAP1 in endothelial cells identified downregulated genes which correspond to cell cycle/cell proliferation events, the specification does not provide any relationship

between any genes involved in inflammation being downregulated upon overexpression of THAP1 and any relationship between a THAP binding site, THRE, and any gene involved in inflammation. The establishment of the relationship of THAP with a regulatory region that controls expression of a gene involved in inflammation needs to be made because nothing in the art or the specification establishes any biological relationship between THAP and inflammation. Further, nothing in the specification provides any guidance that THRE controls any inflammation-related genes. It is unclear, based on the specification, for example, whether the downregulation of cell cycle/cell proliferation genes resulted from THAP interaction with the regulatory regions of these genes or from a secondary effect (e.g. THAP protein sets off a cascade of other, not yet characterized, events). With regard to the broad scope of any THAP-family member, the specification does not provide guidance that other THAP-family members have the ability to bind to DNA, particularly, THRE, and no guidance was provided as to whether any of the THAP proteins have any transcriptional activity. While the specification teaches that amino acids were conserved in proteins comprising putative THAP domains, it is unclear whether these amino acids are necessary for DNA binding, and more particularly, THRE binding (specification, Figure 9C). With regard to arriving at a method measuring changes in expression of a THAP responsive gene, nothing in the specification provides any guidance as to whether any THAP protein has any transcriptional activity (or repressor activity) such that an artisan can monitor changes in gene

transcription. Subsequently, an artisan cannot arrive at any biologically active fragment of a THAP-family member.

As such, the specification does not provide sufficient guidance to arrive at the claimed invention.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of

document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

JH

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER

10/733,878
Application No.:

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- [ ] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [ ] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [ ] 7. Other: _____

Applicant Must Provide:

- [X] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- [X] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- [X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

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